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## Subject: Voretigene Neparvovec-rzyl (Luxturna) Injection

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### DESCRIPTION:

Voretigene neparvovec-rzyl (Luxturna) is an adeno-associated virus vector-based gene therapy that was first approved by the U.S. Food and Drug Administration (FDA) in December 2017 for the treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy. Voretigene neparvovec-rzyl was previously granted orphan designation for this same indication in March 2015. The approval marked a significant medical advancement being the first in vivo gene therapy to be approved in the U.S. Gene therapies are treatments that change the expression of genes to treat disease, for example, by replacing or inactivating a gene that is not functioning properly or by introducing a new gene. Genes are introduced into human cells through a vector, usually a virus such as an adeno-associated virus (AAV). The eye has been an attractive target for gene therapy due to the immune privilege (i.e., tolerance to introduction of antigens without eliciting an inflammatory immune response) provided by the blood-ocular barrier and the minimal amount of vector needed.

Inherited retinal dystrophies (IRDs) are a diverse group of disorders with overlapping phenotypes caused by mutations in any one of more than 220 different genes, and are characterized by progressive degeneration and dysfunction of the retina. The most common subgroup is retinitis pigmentosa (RP), characterized by a loss of retinal photoreceptors. The primary symptoms are night blindness (nyctalopia) and loss of peripheral vision. These losses lead to difficulties in performing visually dependent activities of daily living such as orientation and navigation in dimly lit areas. Visual acuity is typically maintained longer than peripheral vision; however, eventually most individuals progress to vision loss. A less common but more severe inherited retinal dystrophy, Leber congenital amaurosis (LCA), sometimes considered a retinitis pigmentosa subtype, is characterized by an earlier onset, more rapid progression, and

nystagmus. Both RP and LCA have subtypes related to pathogenic biallelic mutations in the RPE65 (retinal pigment epithelium–specific protein 65-kD) gene, which are named RP type 20 and LCA type 2, respectively. There are also other rare IRD phenotypes associated with biallelic mutations in the RPE65 such as Severe Early Childhood-onset Retinal Dystrophy (SECORD). Biallelic RPE65 mutation-associated IRD is very rare and affects approximately 1,000 to 2,000 patients in the U.S. The RPE65 gene encodes all-trans retinyl ester isomerase, an enzyme found in the retinal pigment epithelium where it plays a critical role in the regeneration of light-reacting proteins in the retina. Individuals with biallelic variations in RPE65 lack or have low levels of functional RPE65 enzyme which leads to build-up of toxic precursors, loss of photoreceptors, and eventually complete blindness. Voretigene neparvovec-rzyl delivers a normal copy of the gene encoding RPE65 to cells of the retina, which then facilitates normal protein production to allow phototransduction and restoration of vision loss. Prior to the approval of voretigene neparvovec-rzyl, supportive care was the only management option for these patients.

The efficacy and safety of voretigene neparvovec-rzyl leading to FDA approval was evaluated in an open-label, two-center, randomized trial. Patients ages 3 or older with biallelic RPE65 mutation-associated retinal dystrophy, visual acuity (VA) worse than 20/60 and/or a visual field (VF) less than 20° in any meridian, and with sufficient viable retinal cells were randomized 2:1 to intervention (n=21) or control (n=10). Because of safety concerns, mainly related to the subretinal injection procedure, only subjects who had significant vision loss (as defined in the inclusion criteria) were enrolled. One subject discontinued from the study prior to treatment. Ten subjects were randomized to the control (non-intervention) group. One subject in the control group withdrew consent and was discontinued from the study. The nine subjects who were randomized to the control group were crossed over to receive subretinal injection of voretigene neparvovec-rzyl after one year of observation. The average age of the 31 randomized subjects was 15 years (range 4 to 44 years), including 64% pediatric subjects (n=20, age from 4 to 17 years) and 36% adults (n=11). The 31 randomized subjects included 13 males and 18 females. Bilateral subretinal injections were administered sequentially in two separate surgical procedures with an interval of 6 to 18 days. Efficacy was established on the basis of multi-luminance mobility testing (MLMT) score change from baseline to Year 1. The MLMT was designed to measure changes in functional vision, as assessed by the ability of a subject to navigate a course accurately and at a reasonable pace at different levels of environmental illumination. The MLMT was assessed using both eyes and each eye separately at one or more of seven levels of illumination, ranging from 400 lux (corresponding to a brightly lit office) to 1 lux (corresponding to a moonless summer night). Each light level was assigned a score code ranging from 0 to 6. A higher score indicated that a subject was able to pass the MLMT at a lower light level. A score of -1 was assigned to subjects who could not pass MLMT at a light level of 400 lux. The MLMT of each subject was videotaped and assessed by independent graders. The MLMT score was determined by the lowest light level at which the subject was able to pass the MLMT. The MLMT score change was defined as the difference between the score at baseline and the score at Year 1. A positive MLMT score change from baseline to Year 1 visit indicated that the subject was able to complete the MLMT at a lower light level. Additional clinical outcomes were also evaluated, including full-field light sensitivity threshold (FST) testing, visual acuity, and visual fields.

Table 1 summarizes the median MLMT score change from baseline to Year 1 in the voretigene neparvovec-rzyl treatment group as compared to the control group. A median MLMT score of 2 or greater was observed in the voretigene neparvovec-rzyl treatment group, while a median MLMT score change of 0 was observed in the control group, when using both eyes or the first-treated eye. An MLMT score change of two or greater is generally considered a clinically meaningful benefit in functional vision.

**Table 1: MLMT Efficacy Results at Year 1 Compared to Baseline**

Efficacy Outcomes	Luxturna (n=21)	Control (n=10)	Difference	P-value
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MLMT score change for bilateral eyes, median (min, max)	2 (0, 4)	0 (-1, 2)	2	0.001
MLMT score change for first-treated eye, median (min, max)	2 (0, 4)	0 (-1, 1)	2	0.003

Table 2 shows the number and percentage of subjects with different magnitudes of MLMT score change using both eyes at Year 1. Eleven of the 21 (52%) subjects in the voretigene neparovvec-rzyl treatment group had an MLMT score change of two or greater, while one of the ten (10%) subjects in the control group had an MLMT score change of two.

**Table 2: Magnitude of MLMT Score Change Using Both Eyes at Year 1**

Score Change	Luxturna (n=21)	Control n=10
-1	0	3 (30%)
0	2 (10%)	3 (30%)
1	8 (38%)	3 (30%)
2	5 (24%)	1 (10%)
3	5 (24%)	0
4	1 (4%)	0

Twenty-seven (27/41, 66%) subjects had ocular adverse reactions that involved 46 injected eyes (46/81, 57%). Adverse reactions among all subjects in who have been treated (n=41) are seen Table 3. Adverse reactions may have been related to voretigene neparovvec-rzyl, the subretinal injection procedure, the concomitant use of corticosteroids, or a combination of these procedures and products.

**Table 3: Adverse Reactions Associated with Voretigene Neparovvec-rzyl Administration**

Adverse Reactions	Subjects (n=41)	Treated Eyes (n=81)
Any ocular adverse reaction	27 (66%)	46 (57%)
Conjunctival hyperemia	9 (22%)	9 (11%)
Cataract	8 (20%)	15 (19%)
Increased intraocular pressure	6 (15%)	8 (10%)
Retinal tear	4 (10%)	4 (5%)
Dellen (thinning of the corneal stroma)	3 (7%)	3 (4%)
Macular hole	3 (7%)	3 (4%)
Subretinal deposits	3 (7%)	3 (4%)
Eye inflammation	2 (5%)	4 (5%)
Eye irritation	2 (5%)	2 (2%)

Eye pain	2 (5%)	2 (2%)
Maculopathy (wrinkling on the surface of the macula)	2 (5%)	3 (4%)
Foveal thinning and loss of foveal function	1 (2%)	2 (2%)
Endophthalmitis	1 (2%)	1 (1%)
Foveal dehiscence (separation of the retinal layers in the center of the macula)	1 (2%)	1 (1%)
Retinal hemorrhage	1 (2%)	1 (1%)

### **POSITION STATEMENT:**

The administration of voretigene neparvovec-rzyl (Luxturna) **meets the definition of medical necessity** when **ALL** of the following criteria are met (“1”, “2”, “3”, “4”, and “5”):

1. Member has confirmed biallelic RPE65 mutation-associated retinal dystrophy as defined by either of the following (“a” or “b”) - documentation of the genetic test results must be submitted:
  - a. Single RPE65 pathogenic or likely pathogenic variant found in the homozygous state
  - b. Two RPE65 pathogenic or likely pathogenic variants found in the trans configuration (compound heterozygous state) by segregation analysis when possible\*

*\*If the patient is adopted, or both parents are deceased, segregation analysis may not be possible. In these situations, the two identified RPE65 pathogenic or likely pathogenic variants can be assumed to be in trans- configuration if an inherited retinal disease specialist confirms that the phenotype in the patient matches the gene’s disease association with a high degree of specificity.*
2. Member has sufficient viable retinal cells as determined by optical coherence tomography (OCT) and/or ophthalmoscopy indicated by **ANY** of the follow criteria (“a”, “b”, or “c”) - documentation of the OCT and/or ophthalmoscopy results must be submitted:
  - a. An area of retina within the posterior pole of greater than 100 µm thickness shown on OCT
  - b. Three or more disc areas of retina **without** atrophy or pigmentary degeneration within the posterior pole
  - c. Remaining visual field within 30° of fixation as measured by III4e isopter or equivalent
3. The member is 12 months of age or older
4. The member has not previously received gene therapy (including voretigene neparvovec-rzyl) in their lifetime for a given eye for the treatment of biallelic RPE65 mutation-associated retinal dystrophy
5. The dosage of voretigene neparvovec-rzyl does not exceed  $1.5 \times 10^{11}$  vector genomes (vg) as a single 0.3 mL subretinal injection per eye per lifetime of the member

**Approval duration:** 6 months to allow administration of two total doses of voretigene neparvovec-rzyl (one dose per eye)

The administration of voretigene neparvovec-rzyl (Luxturna) is considered **experimental or investigational** for all other indications due to insufficient evidence in the peer-reviewed medical literature to support safety, efficacy, and net health outcomes.

## **DOSAGE/ADMINISTRATION:**

**THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.**

### **FDA-approved**

- Indicated for the treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy. Patients must have viable retinal cells as determined by the treating physician(s).
- The recommended dose for each eye is  $1.5 \times 10^{11}$  vector genomes (vg), administered by subretinal injection in a total volume of 0.3 mL. Perform subretinal administration of voretigene neparvovec-rzyl to each eye on separate days within a close interval, but no fewer than 6 days apart.
- Recommend systemic oral corticosteroids equivalent to prednisone at 1 mg/kg/day (maximum of 40 mg/day) for a total of 7 days (starting 3 days before administration of voretigene neparvovec-rzyl to the first eye), and followed by tapering the dose during the following 10 days. The same corticosteroid dosing regimen applies for the administration to the second eye. If the corticosteroid taper following administration to the first eye is not complete three days prior to the planned administration to the second eye, then the corticosteroid regimen for the second eye replaces the taper for the first eye.
- Prepare voretigene neparvovec-rzyl within 4 hours of administration using sterile technique under aseptic conditions in a Class II vertical laminar flow biological safety cabinet (BSC). The product should be administered in the surgical suite under controlled aseptic conditions by a surgeon experienced in performing intraocular surgery. Review the product labeling for additional information on preparation and administration.

### **Dose Adjustments**

- No dosage adjustments are required for hepatic or renal impairment. Dosage adjustments for other reasons are also not required.

### **Drug Availability**

- Voretigene neparvovec-rzyl is a suspension for subretinal injection, supplied in a 0.5 mL extractable volume in a single-dose 2 mL vial for a single administration in one eye. The supplied concentration ( $5 \times 10^{12}$  vg/mL) requires a 1:10 dilution prior to administration. The Diluent is supplied in two single-use 2-mL vials

## **PRECAUTIONS:**

### **Boxed Warning**

- None

### **Contraindications**

- None

### **Precautions/Warnings**

- **Endophthalmitis:** Endophthalmitis may occur following any intraocular surgical procedure or injection. Use proper aseptic injection technique and monitor for signs and symptoms of infection.
- **Permanent decline in visual acuity:** Monitor for visual disturbances.
- **Retinal abnormalities:** Monitor for macular abnormalities, retinal tears or breaks. Do not inject in the immediate vicinity of the fovea.

- **Increased intraocular pressure:** Monitor and manage intraocular pressure elevations.
- **Expansion of intraocular air bubbles:** Air travel and/or scuba diving are not recommended until any intraocular air bubbles have been absorbed. It may take one week or more following injection for the air bubble to dissipate. A change in altitude while the air bubble is still present can result in irreversible vision loss. Verify the dissipation of the air bubble through ophthalmic examination.
- **Cataract:** Subretinal injection of voretigene neparvovec-rzyl, especially vitrectomy surgery, is associated with an increased incidence of cataract development and/or progression.
- **Prenancy:** Adequate and well-controlled studies have not been conducted in pregnant women. Animal reproductive studies have not been conducted.
- **Pediatric Use:** Treatment is not recommended for patients younger than 12 months of age, because the retinal cells are still undergoing cell proliferation, and voretigene neparvovec-rzyl would potentially be diluted or lost during cell proliferation.

### **BILLING/CODING INFORMATION:**

The following codes may be used to describe:

#### **HCPSC Coding**

J3398	Injection, voretigene neparvovec-rzyl, 1 billion vector genomes
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#### **ICD-10 Diagnosis Codes That Support Medical Necessity**

H35.50	Unspecified hereditary retinal dystrophy
H35.52	Pigmentary retinal dystrophy
H35.54	Dystrophies primarily involving the retinal pigment epithelium

### **REIMBURSEMENT INFORMATION:**

Refer to section entitled [POSITION STATEMENT](#).

### **PROGRAM EXCEPTIONS:**

**Federal Employee Program (FEP):** Follow FEP guidelines.

**State Account Organization (SAO):** Follow SAO guidelines.

**Medicare Part D:** BCBSF has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

**Medicare Advantage:** No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of guideline creation.

### **DEFINITIONS:**

**Gene therapy:** The therapeutic delivery of nucleic acid polymers into a patient's cells as a drug to treat disease.

## RELATED GUIDELINES:

None

## OTHER:

None

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### **COMMITTEE APPROVAL:**

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 04/10/19.

### **GUIDELINE UPDATE INFORMATION:**

03/15/18	New Medical Coverage Guideline.
03/15/18	Update to Position Statement.
07/01/18	Addition of HCPCS code C9032.
01/01/19	Revision: HCPCS code updates. Added J3398, and removed C9032 and J3590.
05/15/19	Review and revision to guideline consisting of updating the position statement and references.